II. REMARKS:

A. Status of the Claims

Claims 1-22 were originally filed with the case. All claims were rejected in an Office Action mailed September 14, 2005. Claims 1-4 were cancelled and claims 5-8 and 14-17 were amended in the Response to Office Action filed on January 17, 2006. Claims 5-22 were rejected in the outstanding Office Action, mailed March 8, 2006. Claims 8 and 17 are amended in the present Response. No claims are added or canceled herein. We thank the Examiner for considering our submissions.

B. The Claims are Enabled under 35 U.S.C. § 112 (2000).

The Examiner rejects claims 5-22 under 35 U.S.C. § 112, first paragraph, on the grounds that they are not enabled by the specification. The Action asserts that the art of targeted gene therapy in the eye for treatment of a specific condition is unpredictable. Applicants respectfully traverse the rejection.

The enablement requirement ensures that key information important to the art will be open to the public sphere. As the Action notes, the inquiry must be guided by factors set forth in *In re Wands*, 858 F.2d 737 (Fed. Cir. 1988). *See also In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). The eight factors listed in *Wands* are (1) the claim breadth, (2) the nature of the invention, (3) the state of the art, (4) the level of ordinary skill, (5) the predictability of the art, (6) the direction provided by the specification, (7) existence of working examples and (8) the quantity of experimentation required to make the invention. In rebutting the Examiner's *prima facie* order of enablement, we must prove the claims are enabled more likely than not, and not beyond a reasonable doubt. *See In re Irons*, 340 F.2d 974, 978 (CCPA 1965).

The present Application discloses a technique for treating dry eye in a post-

menopausal patient by incorporating coding sequence for the enzyme 15-lipoxygenase in the patient's ocular cells. 15-lipoxygenase is an upstream precursor to 15(s)-HETE, a molecule that stimulates the synthesis of mucin (MUC-1), a crucial compound for eye lubrication. The inventors have discovered that post-menopausal women do not express sufficient levels of 15-lipoxygenase.

The Action's main objection seems to stem from the use of prophetic examples. *See, e.g., Atlas Power Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569 (Fed. Cir. 1984). The use of prophetic examples goes to the fifth factor, the predictability of the art. *Wands*, 858 F.2d at 737. In fact, a majority of the Action's position relates to the assertion that there is no reasonable predictability for this type of gene therapy. The other factors are largely minimized for the purpose of the *Wands* analysis. *Id.*

In asserting that gene therapy is largely unpredictable, the Action relies on older reviews of the gene therapy literature. Pfeifer and Verma, *Gene Therapy – Promises and Problems*, 2 Ann. Rev. Genomics & Hum. Genetics 177; Verma and Somia, *Gene Therapy – Promises, Problems and Prospects*, 389 Nature 249 (1997). Verma *et al.* and Pfeiffer *et al.* are said to provide a review of various vectors known in the art for use in gene therapy and problems associated with each implying that at the time of the claimed invention, resolution to vector targeting had not been achieved in the art. (Action, page 6). The authors of these papers are said to have suggested that more efficient and safe vectors are required to deliver gene to the target cell for therapeutic effective levels of gene expression.

Although Pfeifer appears to express some skepticism about adenoviral and retroviral means of delivery, he admits that both types have been used with success. Pfeifer, *supra.* In addition, the two years between 2001 and 2003 saw a flurry of activity

in the gene therapy field. *See, e.g., Viral Vectors for Gene Therapy: Methods and Protocols*, (Curtis A. Machida ed., 2002); Alexander Pfeifer *et al., Delivery of the Cre Recombinase by a Self-Deleting Lentiviral Vector: Efficient Gene Targeting* In Vivo, 98 Proc. Nat'l Acad. Sci. 11450 (2001).

The Action principally relies on an assertion that "more efficient and safe vectors are required to deliver gene to the target cell for a *therapeutic* effective level of gene expression". (Office Action Communication at 6, Mar. 8, 2006). However, a detailed examination of the Pfeifer 2001 survey fails to yield such an assertion by Pfeifer and Verma. Pfeifer, *supra* at 201. Instead, Pfeifer notes that gene therapy will only be "added to the daily-use therapeutical arsenal", that is, by patients and doctors in the market, if, *inter alia*, geneticists identify target genes, cell biologists optimize gene transfer, virologists develop "efficient and safe vectors" and clinicians carry out safe clinical trials. *Id.* The brunt of Pfeifer's assertions appears to go to clinical safety, a matter under FDA jurisdiction, and not patentability, which must operate under a different standard. In fact, the phrase "[medical] daily use" specifically implies that the threshold of common and reliable experimental use in the art had already been broached as of 2001. (Office Action Communication at 6, Mar. 8, 2006); *cf.* Pfeifer, *supra*.

Moreover, safety is not a concern of patentability. *See cf.* 35 U.S.C. §§ 101-12. In fact, Pfeifer appears to assert that the art of gene therapy had progressed rapidly and reliably between 1997 and 2001. Based on the glut of new ideas in the art between 2001 and 2003, Pfeifer's implication of rapid improvement points to the direction of enablement by prior art.

The best example of enablement by prior art is the Cuthbertson patent, distinguished by the Action. U.S. Patent No. 6,204,251 (issued Mar. 20, 2001). The

Action distinguishes Cuthbertson on the grounds that effecting expression in ocular cells is not enabling to treat a *disease*, and that Cuthbertson is said to teach gene therapy for non-human animals only.

However, Cuthbertson states clearly that the method claimed is for treating an "ocular disease" in an "in situ ocular cell," that is, *in vivo*. Cuthbertson at 10. This contradicts the Action's reading of Cuthbertson as a "general method for effecting expression of an exogenous gene in ocular cells." (Office Action Communication at 9, Mar. 8, 2006). It should be noted that an issued patent must be presumed valid, that is, it should be assumed that it meets the requirements of enablement, definiteness, novelty and non-obviousness. The Action's analysis of Cuthbertson appears to read limitations into the claims that are not there and to provide construction of the issued patent that is better left to a court. For purposes of an evaluation of patentability, it is submitted that this issued patent must be considered to enable what it presumes to teach and that is gene therapy in ocular tissues. It may be true that Cuthbertson lacks enough teaching with respect to specific gene targets that it cannot be said to enable the use of any particular gene sequence for gene therapy. Nevertheless, it can be taken as evidence that gene therapy was a known method of treatment and that its use was believed to be effective at the time of filing of the present application.

The Action relies on three pieces of literature to support its position that viral delivery is ineffective. Keith R. Martin *et al.*, *Gene Delivery to the Eye Using Adeno-Associated Viral Vectors*, 28 Methods 267 (2002); Ashley Behrens *et al.*, *Retroviral Gene Therapy Vectors for Prevention of Excimer Laser-Induced Corneal Haze*, 43 Investigative Ophthalmology & Visual Sci. 968 (2001); Yuko Kamata *et al.*, *Adenovirus-Mediated Gene Therapy for Corneal Clouding in Mice with Mucopolysaccharidosis Type*

VII, 4 Molecular Therapy 307 (2001).

Both Behrens and Kamata appear to describe successful *in vivo* gene transfer by topical treatment and injection. Behrens, *supra*; Kamata, *supra*. Behrens further emphasizes the rapid improvement in the art of gene therapy between 2001 and 2003. The Martin paper appears to describe techniques for transfecting retinal cells. Martin, *supra*. Yet somehow, in reading Martin, the Action concludes that adenovirus treatment of ocular disorders is not enabled for humans. (Office Action Communication at 10, Mar. 8, 2006). In so doing, the Action relies on the language "success with disease models involving cells other than [retinal] cells has been . . . limited". Martin, *supra* at 268. This statement seems to support the notion that gene therapy was believed to be effective, at least in retinal cells, at the time of filing of the present application.

Martin further explains that what the art needs is "optimization" of methods to "target appropriate genes". *Id.* This is in fact the source of the present inventors' innovation – the knowledge that 15-lipoxygenase is a protein responsible for dry eye in menopausal women.

The Action asserts that the predictability of the prior art cannot be extrapolated to human therapy. (Office Action Communication at 11, Mar. 8, 2006); Cuthbertson, *supra*; Behrens, *supra*; Martin, *supra*; Kamata *supra*; Stephen U. Stechschulte, *Rapid Ocular Angiogenic Control via Naked DNA Delivery to Cornea*, 42 Investigative Ophthalmology & Visual Sci. 1975 (2001). However, at least Cuthbertson describes and claims "a method of treating ocular disease" via incorporation of a nucleic acid into an in situ ocular cell, without limitation to the species that is treated. Cuthbertson, *supra* ("'Animal', as used herein includes both humans and other animals and organisms" col. 8, lines 16-17).

Finally, the Action argues that it would require undue experimentation by the skilled artisan in order to develop or design a suitable vector and practice the claimed method due to the unpredictability of the art. It is submitted that Applicants have sufficiently established that gene therapy, as a means of delivering therapeutic gene sequences to the eyes of patients, was believed to be a viable treatment at the time the present application was filed. Furthermore, the fact that some experimentation may be necessary does not preclude enablement. *Atlas Powder Co. v. E.I. duPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed.Cir.1984). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* The invention is directed to the treatment of dry eye in post-menopausal women by delivering a nucleic acid having a specified sequence. The present specification provides the identification of a gene involved in the occurrence of dry eye in post-menopausal women, the sequence of that gene, and a description of methods for delivery of that gene. The experiments for determining optimum delivery conditions, compositions, etc. are routine to the skilled artisan. Thus, it is believed that the claimed invention is enabled.

In light of the foregoing arguments, Applicants respectfully request that the enablement rejection be withdrawn.

C. <u>The Claims are Definite</u>

The Action next rejects claims 8 and 17 under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Action asserts that claims 8 and 17 lack antecedent basis for the limitation "exogenous nucleic acid." Applicants submit that the indefiniteness rejection is moot in light of the amendments to claims 8 and 17. Therefore,

withdrawal of the rejection is respectfully requested.

D. Conclusion

This is submitted to be a complete response to the outstanding Action. The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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